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AUTHOR Corwin, Thomas R; Mancini, Michael
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ABSTRACT

A new test designed to detect an hereditary eye disease called retinitis pigmentosa (RP) is described. This condition is revealed by pigmentation in the retina, but early diagnosis is difficult because the symptoms are subtle, and since it is genetically recessive it frequently occurs in families with no history of early blindness. In many cases RP results in gradual loss of vision and eventual blindness. The test for this problem is in a developmental stage and involves electrical signals picked up from a contact lens electrode placed on the subject's cornea. The responses of the eye to brief flashes of light may thus be recorded and charted and compared to those of subjects with normal vision. (JD)

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A PSYCHOPHYSICAL TEST FOR RETINITIS PIGMENTOSA

Paper presented at
Fifth Annual Meeting
Genesee Valley Psychological Association
Rochester, New York
October 20, 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION & WELFARE
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Thomas R. Corwin
Michael Mancini

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This talk is about a research project we have been working on for the past few months at NTID and at the U. of R. We are just a few months into what will be a three-year project, but we have some preliminary data to show you today which we believe is suggestive of future trends.

Our goal is to develop a new kind of eye-test -- one which will provide early detection of young people with a hereditary eye disease called retinitis pigmentosa, or RP. In many cases the disease is not diagnosed until the patient is in his late teens or early twenties at which point an ophthalmologist can see pigmentation on the retina. The patient gradually develops tunnel vision, becomes unable to see in dim light, and in many cases eventually loses all of his useful vision. RP is hard to diagnose for several reasons: first, it has a very gradual onset, and so patients very often fail to recognize that their vision is deteriorating. Second, the most common form of the disease is genetically recessive, which means that it frequently occurs in families with no history of early blindness or other eye-problem.

For these reasons, RP patients frequently don't know they have the disease until their vision has already deteriorated quite a bit. At this point, an ophthalmologist can see a speckled pattern of dark blotches on the patient's retina when he examines the retina with an ophthalmoscope. But in the early stages of the disease, the retina looks quite normal. Furthermore, in the early stages of the disease, the patient has normal visual acuity, meaning that he has no difficulty in passing conventional eye-chart tests, in which the patient has to read rows of letters.

Our project is to try and find a test that early RP patients will fail, and that would be easy to administer to large groups of people. The necessity for this is that RP (like all hereditary disorders) is fairly rare -- it affects only about one person in 4,000. Therefore we need to test a large sample of people to find potential RP patients. If an effective test were discovered it would then be possible to screen everyone, and identify all potential RP patients. This would provide ophthalmologists with a population of people to use as subjects in experimental tests of treatments. Also, this information would be useful to patients in making vocational decisions and in genetic counseling.

What kind of eye-test might be able to identify early RP patients? Since their acuity is normal and their retinas look normal, we cannot use conventional acuity tests or retinoscopy. In what way are early RP patients abnormal then? A clue comes from a few early RP patients who happen to have had electroretinograph, or ERG, measurements taken. These are electrical signals picked up from a contact-lens electrode placed on the

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subject's cornea. When a subject looks at a very brief, intense flash of light, the electrode picks up a small electrical response from the eye, which is then amplified and put out on a chart recorder. The ERG is a good way to test for advanced cases of RP, because the ERG response is abnormally small in these cases, and it may even be zero. The ERG can also identify cases of early RP. In those early RP patients who have been tested, their ERG's turn out to have normal amplitudes (sizes), but they are abnormal in a subtle way -- they are abnormally sluggish: that is, the responses take longer to build up after the light flash starts, and they may also take longer to die out after the flash goes off, compared to ERG's from a normal eye. This fact from the clinic gave us the idea to measure how well subjects respond to sudden changes in light level. Because of the ERG data, we expected that early RP patients might have trouble detecting luminance changes. So, we came up with a series of five tests, each one requiring the subject to respond to a target which changes in luminance. We plan to try each of these tests on NTID and U. of R. students, to see how well the tests distinguish between subjects known to have RP and a control group of subjects without RP.

Today we are reporting some results of the first test we have tried, involving a flickering target. We have run 10 people on this test so far: five with normal vision, and five people who have been diagnosed as having RP. The data you will see in a moment shows that our test may be a good one, because it turns out that there are some differences in how our two groups performed.

Let me start by describing how the flicker test works. The subject sits down in front of an ordinary oscilloscope screen, which is uniformly filled with light. When the observer is ready, the screen slowly begins to change in brightness in a sinusoidal manner, that is, for one second it becomes brighter than the initial level, then it reverses, returns to the initial level; for one second it becomes darker than the initial level, returns to the original level, and so on, until the observer responds that he sees the flicker. Now when the amplitude of the luminance-changes are fairly large, so that the screen luminance is changing back and forth by several percent, most observers have no trouble detecting the flicker even when it is slow: (1 cycle every 2 seconds). As the amplitude of the luminance-changes becomes smaller, of course the flicker becomes harder and harder to see. So to measure our subject's sensitivity, we systematically reduce the amplitude of the luminance changes, starting at several percent and proceeding down to perhaps less than a tenth or one one-hundredth of a percentage-point, until our subject cannot discriminate between the flicker and a steady screen. At that point, we change the flicker rate, from one cycle every two seconds to one cycle every second, and measure sensitivity again. We repeat this for 8 different flicker rates from 1/2 to 32 cycles per second. We then make up a flicker sensitivity curve by plotting sensitivity against flicker rate. Gathering enough data for one curve takes about 20 minutes the way we are doing it now, but when we automate the procedure later, we expect to be able to get the same data in less than 10 minutes.

The flicker sensitivity curve contains several sources of information about the subject's visual sensitivity.

SLIDE 1 shows a series of flicker sensitivity curves, measured in two laboratories under various experimental conditions using subjects with normal vision. The horizontal axis is the flicker rate expressed in cycles per second, or Hertz, units: the range extends from 1 Hz to above 50 Hz. The vertical axis is a measure of the observer's sensitivity in detecting the flicker expressed in modulation units. Modulation is basically the contrast of the flicker as it varies over time: specifically it's 1/2 the difference between the brightest and the darkest phase of the flickering light required for the subject to see the flicker, divided by the mean luminance of the light source (that is, the intensity the source would have if it weren't flickering). In these curves, the modulation ranges from 100% down at the bottom to 1/2% at the top. The different curves plotted are for different intensity sources, from very dim at the lower left, to quite intense at the upper curves. Note that the effect of intensity is to shift the relative sensitivity upwards, except for bunching up at slow flicker rates, where intensity does not seem to matter very much. The curves on the right were measured on a small (2 degree) flickering field, surrounded by a larger illuminated field which was not flickering. Here the curves have the same general U-shapes, and show similar bunching up at slow flicker rates, but the left sides of the curves are relatively higher: reducing the size of the flickering field seems to increase sensitivity to slow flicker rates.

Another interesting fact is that the peaks of these curves shift as the intensity of the flickering light-source is reduced. For the most intense sources, peak sensitivity is at about 20 Hz, but when the light source is made less intense, the peak sensitivity shifts to about 10 Hz.

So, I think you can see that these curves are sensitive to changes in experimental conditions in several ways. This is why we think these measurements might also be sensitive to the subtle abnormalities in the visual systems of people in the early stages of RP.

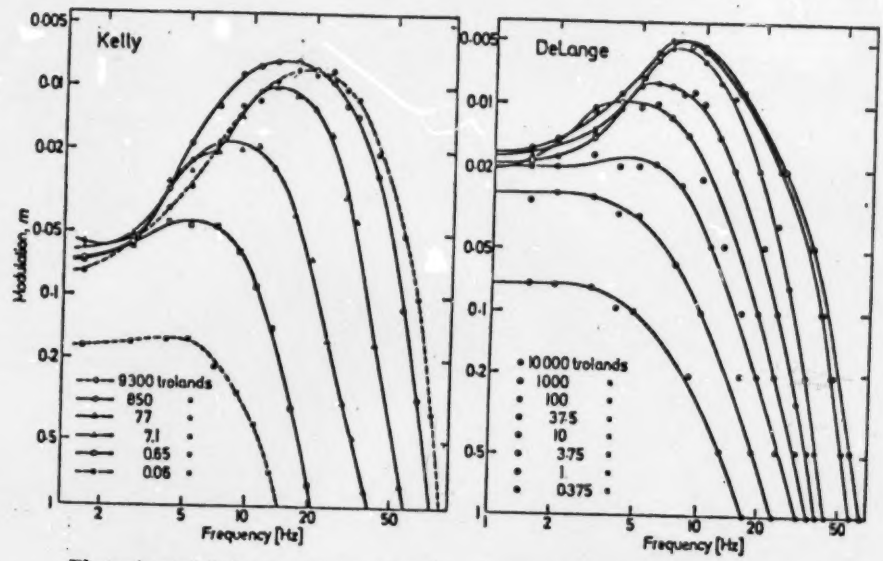
As I said before, we have so far measured flicker sensitivity curves for 5 young people who are suspected of having RP, and we made the same measurements on five control subjects. The individual results of all these measurements are shown in SLIDE 2. As you can see, all of our subjects have the characteristic inverted-U shaped sensitivity curve. All of the 5 control subjects, plotted on the left side of the slide, showed the best sensitivity to a flicker rate of 8 Hz. Two of our RP subjects also had a peak sensitivity for 8 Hz flicker, but two of them had peaks at only 4 Hz. This effect is analogous to the previous slide for normal subjects where a reduction in intensity produced a shift in sensitivity to lower frequencies. We think that this may be an important difference between the groups, and we plan to follow up on this possibility in future testing sessions. But right now the difference is not reliable, because we can't locate the peak with any precision using only 7 different test frequencies. In later tests, we plan to measure more values in the middle of the frequency range so that we can pin-point the frequency yielding peak sensitivity for each subject. One of the RP subjects we tested had sensitivities considerably lower than the other three, so we have treated this case separately. This individual was significantly less sensitive than either the controls or other RP's. At this point we don't know why this individual is so different from the others, but we are pleased that at least one early RP subject would be very easy to detect with a flicker test. In the next slide we have plotted the averaged data. SLIDE 3 please. Looking at the upper RP curve, I think you can see that there may be a

tendency to a difference in sensitivity between our two groups. The curves of the RP group (labeled N = 3) tend to have a slightly lower overall sensitivity level than the control group. The average difference between the two groups is about 4 1/2 dB which corresponds to a factor of 3.5 in modulation. The lower RP curve however lies 25 1/2 dB below the others, which is a factor of 350 in modulation. There is no doubt that this RP subject is abnormal on our test.

Another difference that may exist between the two upper curves involves the slope of the curves on the right-hand side. The high-frequency slope of the upper RP curve tends to be a bit shallower than the control group's. Numerically, the loss of sensitivity as flicker increases from 16 Hz to 32 Hz is twice as rapid in the normal group than in the RP group.

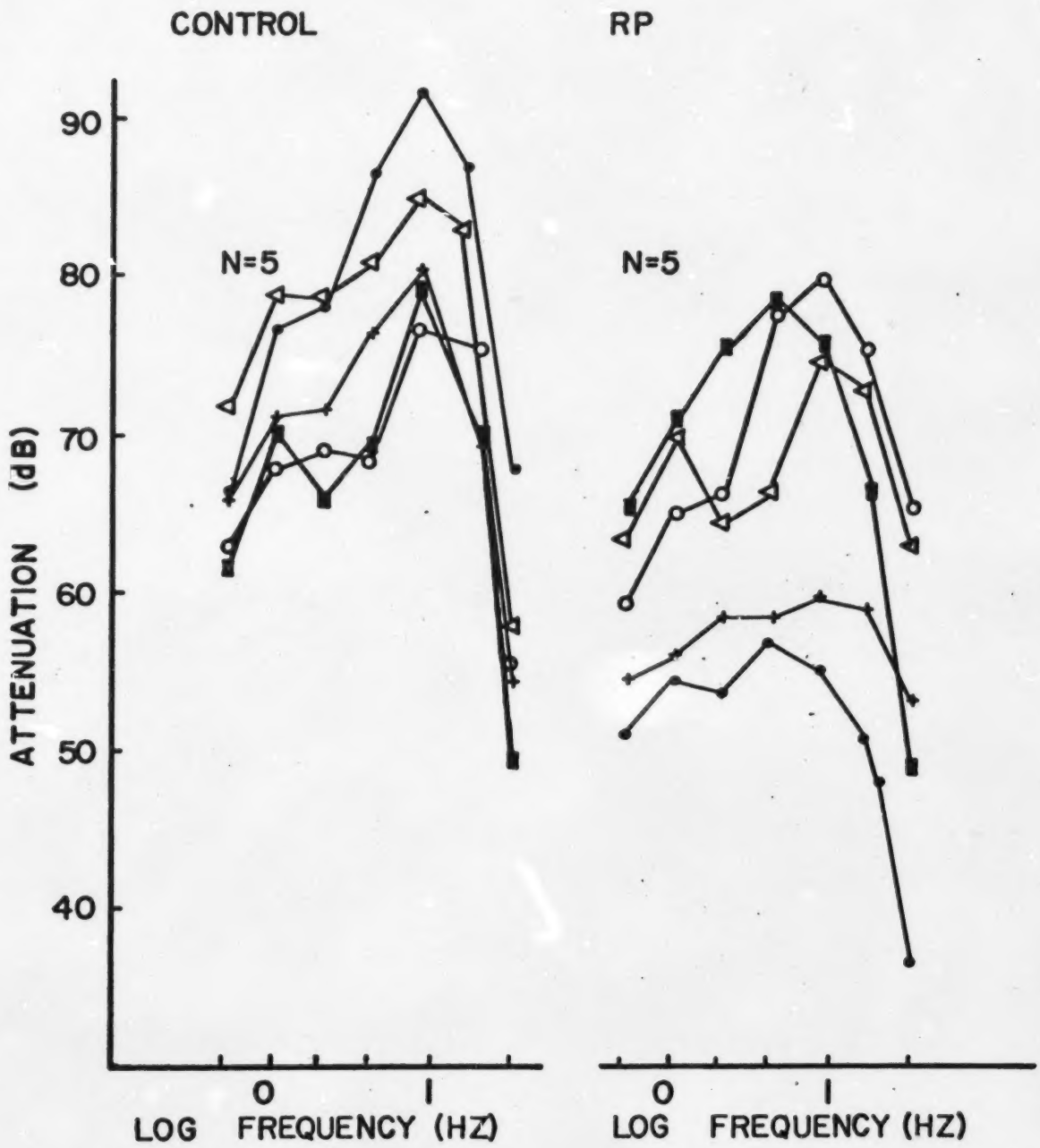
So, in summary, we think we have a test which may be effective in identifying RP patients from the general population. We think tentatively that the flicker sensitivity curve of an RP patient may turn out to be abnormal in one or more of the following ways: (1) The curve may be abnormally lower at all frequencies, (2) the slope of the curve's high-frequency portion may be abnormally shallow, and (3) the point of maximal sensitivity may occur at an abnormally slow flicker rate.

As we test more and more subjects and correlate their pattern of flicker sensitivity with other measures of their visual systems, we hope to be able to specify which of these factors will be the best predictor of early RP.



Photopic modulation sensitivity data. The curves on the left were obtained with a large flickering field; those on the right with a small flickering spot on a steady surround (KELLY, 1961a; DELANGE, 1958a)

SLIDE 1


CONTROL
RP
N=5
N=5
90
80
70
60
50
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ATTENUATION (dB)
0
1
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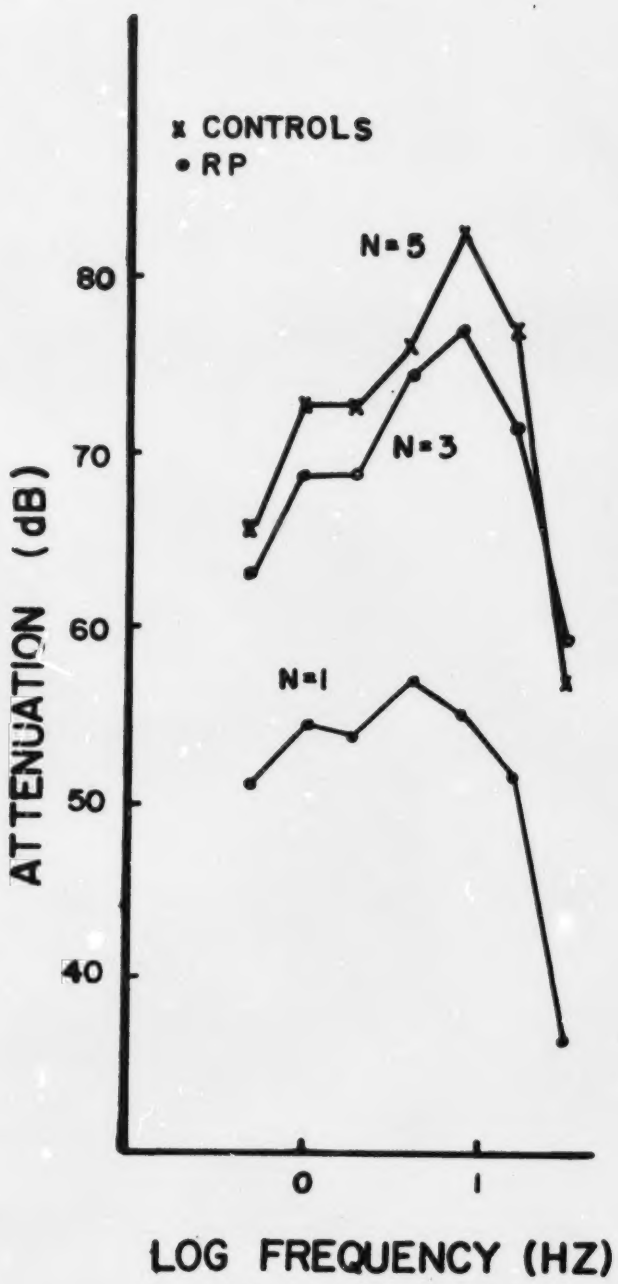
LOG FREQUENCY (HZ)

SLIDE 2


x CONTROLS
• RP
N=5
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80
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ATTENUATION (dB)
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SLIDE 3